

REMARKS

Status Summary

Claims 1-3, 6, and 8 are pending in the present U.S. patent application as a result of a Restriction/Election Requirement, and have been examined by the United States Patent and Trademark Office (hereinafter "the Patent Office").

Claims 1-3, 6, and 8 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Liu *et al.* (88 *J Pharmaceutical Sci* 1161-1168, 1999; hereinafter "Liu") in view of U.S. Patent No. 5,144,045 to Wissner et al. (hereinafter "Wissner").

The specification has been amended to correct a typographical error in the filing date of the priority document that appears in the "Cross Reference to Related Applications" paragraph. No new matter has been added as a result of the amendment to the specification.

Claim 3 has been canceled. Claim 2 has been amended. Certain members recited in the Markush Group have been canceled as being drawn to non-elected subject matter. The claim has also been amended to recite the general structure of the claimed alkylphosphocholines. Support for the amendment can be found throughout the specification as filed, including *inter alia* at page 14, lines 5-8. Additional support can be found in Figure 2A.

Reconsideration of the application based on the remarks set forth below is respectfully requested.

Response to Claim Rejection - 35 U.S.C. § 103(a)

Claims 1-3, 6, and 8 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Liu in view of Wissner. According to the Patent Office, Liu teach an alkylphosphocholine for enhancement of paracellular permeability to overcome the barrier to absorption of orally administered drugs posed by tight junctions in the intestinal epithelium. The Patent Office also asserts that applicants have stipulated that Wissner teach the synthesis of phosphocholines and that alkylphosphocholines (APCs) are known in the art as inhibitors of phospholipase C (PLC). And finally, the Patent Office asserts that Wissner teaches oral delivery of phosphocholine derivatives. After

Careful consideration of the rejection and the Patent Office's basis therefor, applicants respectfully traverse the rejection and submit the following remarks.

The Patent Office contends that it would have been obvious to one of ordinary skill in the art to enhance permeability of tight junctions in the intestinal epithelium with alkylphosphocholines for the beneficial effect of overcoming the barrier to absorption of orally administered hydrophilic drugs in view of Liu. In support of this contention, the Patent Office asserts that because alkylphosphocholines are known phospholipase C inhibitors, "one of ordinary skill would expect the correlation demonstrated by applicants given Liu et al.'s work". Official Action at page 3.

Initially, applicants respectfully submit that it appears that the Patent Office is relying on the knowledge that alkylphosphocholines are PLC inhibitors to provide the basis for the assertion that it would have been obvious to use PLC inhibitors generally, and alkylphosphocholines specifically, as therapeutics to enhance paracellular permeability. This connection appears to be based on Liu, which is asserted to teach that dodecylphosphocholine (DPC) can improve paracellular permeability across Caco-2 monolayers by modulating tight junctions.

Applicants respectfully submit, however, that this basis does not suffice to support a *prima facie* case of obviousness. Applicants respectfully submit that at the time of filing, it was not known that alkylphosphocholines could enhance paracellular permeability through inhibition of PLC, and that it is only with reference to the instant specification that the Patent Office can conclude that PLC inhibitors as a class can be used for this purpose. Thus, it is only with knowledge of applicants' specification that the Patent Office can assert that any modulating activity is derived from DPC's inhibition of PLC.

Since it was unknown at the time of filing of the instant application that DPC's activity in enhancing paracellular permeability resulted from PLC inhibition, applicants respectfully submit that there is no teaching in Liu that would lead one of ordinary skill in the art to believe that PLC inhibitors generally could be used to enhance paracellular permeability as recited in claim 1. Thus, applicants respectfully traverse the Patent Office's assertion that since alkylphosphocholines were known to be PLC inhibitors,

"one of ordinary skill would expect the correlation demonstrated by applicants' work given Liu et al.'s work". Official Action at page 3. Applicants respectfully submit that Liu's demonstration that DPC enhances paracellular permeability does not compel the conclusion that PLC inhibitors generally, or even alkylphosphocholines generally, would enhance paracellular permeability until it was shown that the activity of DPC derived from its ability to inhibit PLC.

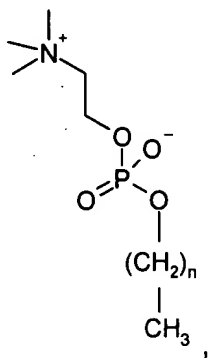
In fact, when taken as a whole, Liu clearly states that compounds that had been shown to enhance intestinal absorption of therapeutic molecules were grouped into two main categories: detergents/surfactants and Ca^{2+} chelators. Other agents, such as lysophosphatidylcholines, medium chain fatty acids, and acyl carnitines, were thought to increase paracellular permeability via a mechanism other than Ca^{2+} chelation, hypothesized in Liu to be via upregulation of intracellular Ca^{2+} . As one of the consequences of PLC inhibition would actually be downregulation of intracellular Ca^{2+} , applicants respectfully submit that Liu in fact teaches away from PLC inhibition as a mechanism of action for DPC.

Summarily, it appears that the Patent Office is rejecting claim 1 over Liu on the basis of a demonstration that DPC enhances paracellular permeability, combined with the knowledge found only in applicants' specification that this property is due to DPC's ability to inhibit PLC. Liu does not suggest this mechanism, and in fact suggests instead that the mechanism might involve upregulation of intracellular Ca^{2+} .

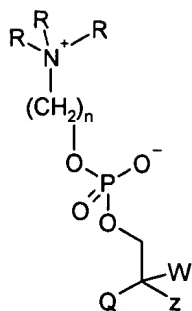
Accordingly, applicants respectfully submit that a *prima facie* case of obviousness has not been presented because the combination of Liu with applicants' specification is improper. As the Court of Appeals for the Federal Circuit stated in *In re Rijckaert*, "obviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established". *In re Rijckaert*, 9 F.3d 1531, 28 USPQ2d 1955 (Fed. Cir. 1993). Additionally, "[o]bviousness cannot be predicated on what is unknown". *In re Spormann*, 363 F.2d 444, 448 (C.C.P.A. 1966). Given this proscription against using later learned information from forming the sole basis of a rejection under § 103, applicants respectfully submit that a *prima facie* case of obviousness has not been presented.

Applicants further respectfully submit that the Patent Office has not presented a *prima facie* case of obviousness of the claims over the combination of Liu and Wissner. Initially, and contrary to the Patent Office's assertion, applicants respectfully submit that Wissner does not teach oral administration of phospholipase C inhibitors. Rather, Wissner clearly discloses inhibitors of phospholipase A₂. Since Wissner does not teach the claimed alkylphosphocholines as inhibitors of PLC, applicants respectfully submit that there is no motivation to combine Liu and Wissner to prepare a PLC inhibitor as an oral therapeutic for enhancing paracellular permeability without reference to the instant specification in which the ability of PLC inhibitors to enhance paracellular permeability is first disclosed. Thus, it appears that the Patent Office is using applicants' specification to provide the motivation to combine Liu and Wissner.

Applicants further respectfully submit that none of the phosphocholine derivatives disclosed in Wissner are alkylphosphocholines as claimed in claim 2 of the instant application. Claim 2 is directed to alkylphosphocholines (APCs) of the following general formula:



wherein n = 9, 10, 12, 13, 14, 15, 16, 17, 18, or 19. As seen above, this general formula relates to straight-chain alkylphosphocholines. Wissner, on the other hand, teaches phosphocholine derivatives that have the following general structure:



Applicants respectfully submit that only when R is methyl, $n = 2$, and C(WQZ) is a straight chained C_9 , C_{10} , or $\text{C}_{12}\text{-C}_{19}$ alkyl would Wissner disclose the instant alkylphosphocholines. Close inspection of Wissner, however, indicates that these conditions are not satisfied by any of the embodiments disclosed.

More specifically, in no case can C(WQZ) be C_9 , C_{10} , or $\text{C}_{12}\text{-C}_{19}$ alkyl. For example, there are dozens of potential structures encompassed by general formula C (shown starting at column 1, line 56 of Wissner). Comparing C with the alkylphosphocholines of the instant application shows that C requires the presence of a branch in the C(WQZ) chain, with one side of the branch (C-Q) necessarily having an amine group and the other side of the branch (C-Z) necessarily containing an ether linkage. Continuing now with D from Wissner, it is apparent that Q must comprise a sulfur group, and can optionally include a sulfur group double bonded to one or more oxygens. Visual inspection of general formula E reveals that embodiments (i)-(xiv) all have groups other than straight chain C_9 , C_{10} , or $\text{C}_{12}\text{-C}_{19}$ alkyl, including additional phosphate groups (i and ii), unsaturated carbon-carbon bonds (iii, iv, and vi), a boron atom (v), additional ether linkages (vii, ix, xi), C=NOH groups (viii), carbonyl bonds (ix, x, xi, xiv), and/or hydroxyl groups (ii, viii, xii, xiii). General formula F involves a β -lactam ring structure between the C, W, and Q. And finally, G has W and Q contained within an isoxazoline ring, and additional ether linkages are present.

Thus, applicants respectfully submit that at best one of ordinary skill in the art would have been confronted with a teaching of Lui that DPC might or might not be useful as a paracellular permeability enhancer, but would not look to Wissner to formulate an oral DPC as an absorption enhancer because Wissner did not teach DPC, or any alkylphosphocholines of claim 2, at all. In fact, the only motivation to look to

Wissner might be derived from the knowledge that PLC inhibitors can be used to enhance paracellular permeability and Wissner teaches oral formulations of PLA₂ inhibitors. The two enzymes PLC and PLA₂ are completely different with respect to their substrates and catalytic reactions, and thus applicants respectfully submit that there is no predictable association between the inhibitors of these two enzymes. Without the connection between PLC and PLA₂, applicants respectfully submit that there is no motivation to combine Liu and Wissner.

However, that DPC works to enhance paracellular permeability through PLC inhibition was not known at the time the instant application was filed, and thus cannot be used to provide the motivation to combine the references. According to the Court of Appeals for the Federal Circuit, "[b]ecause the suggestion to combine or modify references must occur prior to an applicant's date of invention, an unknown inherency cannot supply this suggestion at the required time". *In re Rijckaert*, 9 F.3d at 1534 (emphasis added). Furthermore, "[l]ater 'discovery' of the inherency does not alter the analysis". *Id.* Consequently, applicants respectfully submit that there is no motivation to combine Liu with Wissner as proposed by the Patent Office. Thus, a *prima facie* case of obviousness of the claims has not been presented.

Summarily, applicants respectfully submit that the Patent Office has not presented a *prima facie* case of obviousness with respect to claim 1 or claim 2. Claim 3 has been canceled, and thus the rejection as to this claim is believed to have been rendered moot. As such, applicants further submit that independent claim 1 and dependent claims 2, 6, and 8 are in condition for allowance, and respectfully request that the rejection of claims 1, 2, 6, and 8 under U.S.C. §103(a) be withdrawn and that the claims be allowed at this time.

*Discussion of the Claims with Respect to the
References Cited in the Enclosed IDS*

An Information Disclosure Statement (IDS) is being filed along with the instant Amendment B. In an abundance of caution, applicants respectfully submit the following remarks related to the pending claims in view of the references disclosed in the IDS.

The IDS discloses additional references that have been cited in during the prosecution of the related European patent application. The references cited in Europe are as follows:

- Document D1: Liu (also cited in the instant prosecution)
- Document D2: PCT International Patent Application Publication WO 02/11666 (hereinafter "WO 02/11666")
- Document D3: Higard *et al.* (1999) *Drug News Perspect* 12:69-72
- Document D4: Grunicke *et al.* (1998) *Drugs of Today* 34(Suppl F):3-14
- Document D5: Berkovic *et al.* (1996) *J Exper Therapeut Oncol* 1:302-311
- Document D6: Pawelczyk *et al.* (1993) *Biochemical Pharmacol* 493-497
- Document D7: Cereijido *et al.* (1993) *J Cell Sci Suppl* 17: 127-132
- Document D8: Hashimoto *et al.* (1998) *Biosci Biotechnol Biochem* 1819-1821

With respect to Document D1, applicants respectfully direct the Patent Office's attention to the remarks presented hereinabove, as Document D1 is Liu.

With respect to Document D2, WO 02/11666 was published on February 14, 2002, and thus is not prior art as to the instant patent application.

With respect to Documents D3-D6, these references disclose that alkylphosphocholines are known to be protein kinase C (PKC) and phospholipase C (PLC) inhibitors. These documents refer to alkylphosphocholines loosely to describe a variety of compounds containing different phosphate head-groups including, but not restricted to, 2-trimethylaminoethylphosphate which is supposed to be present in alkylphosphocholine. Hexadecylphosphocholine is the only compound described in these documents that could even possibly be referred to as alkylphosphocholines. Secondly, these documents have attempted to relate the PLC inhibitory activity to anti-tumor activity of the compounds. Nowhere in the references is there any suggestion of the activity of alkylphosphocholines in paracellular permeability or other tight junction-related functions. Since the instant application is the only reference that discloses that

PLC inhibitors generally, and alkylphosphocholines specifically, increase paracellular permeability via their activities as PLC inhibitors, these references do not motivate one of ordinary skill in the art to consider alkylphosphocholines as modulators of paracellular permeability.

Document D7 is asserted by the European Patent Office (hereinafter "the EPO") to disclose that inhibition of PLC reduces transepithelial electrical resistance (TEER), and activation of PLC increases TEER. Document D8 is asserted to also disclose this observation. However, in each case the EPO is overstating the teachings of the references.

With regard to Document D7, the only evidence presented for the involvement of PLC is that TRH (an activator of PLC) increases TEER and neomycin (an inhibitor of PLC) blocks the development of TEER. Initially, applicants respectfully submit that the experiments disclosed in Document D7 relate to the formation of tight junctions, particularly the involvement of G proteins in the formation of tight junctions, and thus are of uncertain value as far as teaching a modulation of the activity of tight junctions that are already formed and present in differentiated enterocytes. This can be seen on page 130 of Document D7, which states that neomycin "blocks the development of" TEER. Additionally, applicants respectfully submit that TRH has numerous effects, activation of PLC being but one of them, and similarly neomycin also has multiple effects on cells including inhibition of PLC via an unknown mechanism that may involve inhibition of PLC secondary to other unknown cellular effects. Taken together, applicants respectfully submit that Document D7 provides at best speculation regarding the role of G-proteins on the formation of tight junctions, and thus at best offers an invitation to experiment. Furthermore, this invitation to experiment fails to provide a reasonable expectation for success, and thus does not support a rejection under 35 U.S.C. § 103.

Turning now to Document D8, this reference discloses experiments designed to investigate the effect of β -lactoglobulin on the stability of tight junctions in Caco-2 monolayers. Document D8 suggests that compound 40/80, which is asserted to be a inhibitor but the structure for which cannot be determined, caused a decrease in TEER that was increased by pre-treatment of the cells with β -lactoglobulin. However,